HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Histological characteristics of early-stage oral tongue cancer in young versus older patients : A multicenter matched-pair analysis

Bello, Ibrahim O.

2020-07

Bello , I O , Almangush , A , Heikkinen , I , Haglund , C , Coletta , R D , Kowalski , L P , Makitie , A A , Nieminen , P , Leivo , I & Salo , T 2020 , ' Histological characteristics of early-stage oral tongue cancer in young versus older patients : A multicenter matched-pair analysis ' , Oral Diseases , vol. 26 , no. 5 , pp. 1081-1085 . https://doi.org/10.1111/odi.13288

http://hdl.handle.net/10138/332715
https://doi.org/10.1111/odi.13288

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Accepted Article

DR IBRAHIM O BELLO (Orcid ID : 0000-0003-2085-3185)

Article type : Short Communication

Histological characteristics of early-stage oral tongue cancer in young versus older patients: a multicenter matched-pair analysis

Ibrahim O. Bello[1, 2], Alhadi Almangush[2,3,4], Ilkka Heikkinen[2], Caj Haglund[5,6], Ricardo D. Coletta[7], Luiz P. Kowalski[8], Antti A. Mäkitie[9,10,11], Pentti Nieminen[12], Ilmo Leivo[3], Tuula Salo[2,13,14]

[1]Department of Oral Medicine and Diagnostic Sciences, King Saud University, Riyadh, Saudi Arabia

[2]Department of Pathology, University of Helsinki, Finland

[3]Institute of Biomedicine, Pathology, University of Turku, Turku, Finland

[4]Faculty of Dentistry, University of Misurata, Misurata, Libya.

[5]Research Programs Unit, Translational Cancer Biology, University of Helsinki, Finland

[6]Department of Surgery; University of Helsinki and Helsinki University Hospital, Finland

[7]Department of Oral Diagnosis, School of Dentistry, University of Campinas, Piracicaba, São Paulo, Brazil

[8] Department of Head and Neck Surgery and Otorhinolaryngology, AC Carmago Cancer Center, Sao Paulo, and Head and Neck Surgery Department, University of Sao Paulo Medical School, Sao Paulo, Brazil

[9]Otorhinolaryngology—Head and Neck Surgery, University of Helsinki and Helsinki University Hospital

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ODI.13288

This article is protected by copyright. All rights reserved

[10]Research Programme in Systems Oncology, Faculty of Medicine, University of Helsinki

[11] Department of Clinical Sciences, Intervention and Technology, Division of Ear, Nose and Throat Diseases, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

[12]Medical Informatics and Data Analysis Research Group, University of Oulu

[13]Oral and Maxillofacial Diseases; University of Helsinki, Finland

[14]Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu

Correspondence:

Dr Ibrahim O. Bello, BDS, PhD

Department of Oral Medicine and Diagnostic Sciences, King Saud University, Riyadh, 11545, Saudi Arabia;

Department of Pathology, University of Helsinki,Haartmaninkatu 3, Helsinki, FIN-00014, Finland

Email: ibello@ksu.edu.sa; ibrahim.bello@helsinki.fi

Keywords: histopathological characteristics; early-stage, oral tongue cancer; young; matched-pair analysis

This article is protected by copyright. All rights reserved

Accepted Article

Accepted Article

Introduction

The mean age of diagnosis of new oral squamous cell carcinoma (OSCC) cases is around 60 years with less than 5% of all patients aged 45 years or younger (Taybos, 2003). Oral tongue squamous cell carcinoma (OTSCC) is the most common, and presents with the worst prognosis (Ng et al., 2017). Several risk factors have been associated with OTSCC, many of which appear to be more related to older age (Farquhar et al., 2018). Young OTSCC patients lack these risk factors or when present, they have much shorter exposure time to the risk factors, suggesting different genomic and molecular changes than seen in older OTSCC patients (Llewellyn et al., 2004).

Globally the increased incidence of OTSCC in the past four decades is partly attributable to increased cases among younger patients, with some countries experiencing up to four fold increase (Muller et al., 2008, Ng et al., 2017). Suggestions for this increase included oncogenic virus infection, exposure to yet unidentified mutagens, alterations in diet or oral microbiome and inherited genetic defects predisposing to OTSCC (Gu et al., 2019). However, conflicting reports about clinical behavior and prognosis of young OTSCC patients compared with older patients abound, as reviewed by different groups (Campbell et al., 2018, Paderno et al., 2018).

Previous studies have focused mainly on the clinical outcome and molecular characteristics, but not on the histopathological characteristics to explain the possible differences and similarities of OTSCC between young and older patients. The purpose of this study was therefore to compare several OTSCC epithelial and stromal histological features with independent prognostic potential like tumour budding (TB), depth of invasion (DOI) and worst pattern of invasion (WPOI) (Almangush et al., 2015, Almangush et al., 2014), tumour-stroma ratio (TSR) (Almangush et al., 2018) and stromal tumour-infiltrating lymphocytes (TIL) (Heikkinen et al., 2019), in addition to routine parameters like

This article is protected by copyright. All rights reserved

tumour grade and perineural invasion (PNI) in patients with early-stage OTSCC between patients ≤45 years and those >60 years.

Methods

A previously studied cohort of 311 patients treated for early-stage (cT1-2N0M0) OTSCC from 1979 to 2009 at six university hospitals in Finland and Brazil was used (Almangush et al., 2018). Only 42 patients were aged ≤ 45 years. These cases were extracted and matched according to the clinical tumour stage (stage I or II), gender and centers of management with patients >60-year-old. Patients aged 46-60 years were excluded because their cancer-related events rate were much more similar to the young patients than the elderly group.

The histopathological features extracted for comparison included those often included in pathology reports such as WHO tumor grade (Kademani et al., 2005), DOI (Brierley et al., 2017), PNI (Brandwein-Gensler et al., 2010), and WPOI (Brandwein-Gensler et al., 2010), in addition to TB (Almangush et al., 2014), TSR (Almangush et al., 2018), TILs (Heikkinen et al., 2019) and histologic risk score (HRS) (Brandwein-Gensler et al., 2010) (Table 1). These histopathologic features were scored as illustrated in Figure 1. The procedures for evaluating the parameters studied are outlined in the published studies (Tam et al., 2019, Almangush et al., 2015, Almangush et al., 2018, Heikkinen et al., 2019, Brandwein-Gensler et al., 2010). Cross-tabulation analysis of the differences in histopathologic characteristics and other variables between paired patients groups were done. Statistical significance was evaluated using McNemar (2x2 tables) or McNemar-Bowker (3x3 tables) tests as the compared groups were not considered independent, since the subjects were chosen based on similar characteristics. IBM SPSS software version 23 was used for statistical analysis.

Results

With minor differences, the WHO grade, depth of invasion and perineural invasion bear close resemblance in both groups (Table 1). Regarding other histological characteristics, the young group had more high-intensity TB (43% vs. 24%) and high HRS (76% vs. 64%) when compared with the

This article is protected by copyright. All rights reserved

Accepted Article

older patients. Similarly, higher WPOI (86% vs. 69%) and TSR (36% vs 31%) were noted more in young patients compared with older patients. Low TIL was observed in 14% of tumours in the young group compared with 17% in the older group. No statistically significant difference was observed between the two groups in all the parameters evaluated (P>0.05) (Table 1).

Discussion

Some workers reviewed the several conflicting reports regarding the prognosis of OTSCC in young patients in comparison to older patients among American patients (Campbell et al., 2018). They adduced several reasons for this incongruity, including lack of statistical power in studies, absence of a control group of older patients, and use of different survival end points thereby making comparison between studies difficult. In general, the more recent studies, with few exceptions, have reported better survival outcome for younger patients but the controversy still lingers (Campbell et al., 2018, Paderno et al., 2018).

We have earlier established that some histopathological characteristics are independently associated with prognosis of early-stage OTSCC patients (Almangush et al., 2014, Almangush et al., 2015, Almangush et al., 2018, Heikkinen et al., 2019). A previous study which compared stromal myofibroblast quantity in matched young and older OTSCC patients found no significant differences between both groups (Fonseca et al., 2014). Increased stromal myofibroblasts has been associated with poor prognosis in OTSCC (Bello et al., 2011). In a previous study, we suggested that stromal myofibroblasts are probably more influential in late-stage OTSCC than early stages (Almangush et al., 2014).

In this present study, no significant differences in the histopathological characteristics of early-stage OTSCC was seen between clinically matched young and elderly groups. Based on this, it is therefore not possible to suggest or conclude that the management protocol for early-stage OTSCC should be different between the two groups. This lack of difference in the histopathological features turns the attention to genomic and molecular differences. Some studies have reported lack of differences in the genomic features between young and older OTSCC patients based on whole exome-

This article is protected by copyright. All rights reserved

Accepted Article

sequencing and copy number analysis (Pickering et al., 2014). However, diverse copy number variations seemed to be related to worse prognostic phenotype within young patients (Gu et al., 2019). DNA ploidy studies have suggested increased genomic instability in young OTSCC patients with increased aneuploidy, tetraploidy and mean higher DNA index noted (Santos-Silva et al., 2011). A recent review on molecular testing concluded that OTSCC is essentially similar in young and older patients (Campbell et al., 2018). Genetic studies are usually limited to a small number of patients, and more needs to be done to establish the true nature of OTSCC in young patients, particularly early-stage disease.

In summary, this study did not find any significant differences in the histopathologic features of early-stage OTSCC between the young (≤ 45 years) and the elderly patients (>60 years) in our multi-institutional series. This invites further validation studies in larger cohorts of early-stage OTSCC. More refined genomic, metagenomics and molecular investigations in these patient groups are also warranted to elucidate whether their treatment protocols should be developed differently.

Compliance with Ethical Standards

This study was approved by the Finnish National Supervisory Authority for Welfare and Health (VALVIRA), the Brazilian Human Research Ethics Committee, and the Ethical Committee of University Hospital of Helsinki, Oulu, Kuopio, Turku, and Tampere in Finland and the A.C. Camargo Cancer Center, São Paulo, Brazil**.**

Conflict of Interest

None declared

Funding Source

This article is protected by copyright. All rights reserved

Accepted Article

Sigrid Juselius Foundation and Finnish Cancer Society

Accepted Article

Author Contributions

IOB, AA contributed to conception, study design and data interpretation. **IH, CJ, RDC, LPK, AAM, IL, TS** contributed to data collection and assembly and interpretation. **PN** did the statistical analysis. **IL, TS** provided logistical support and work integrity. All the authors contributed to the drafting of the article, provided critical revision for important intellectual content, and approved the final version.

References

Almangush A, Bello IO, Coletta RD, Makitie AA, Makinen LK, Kauppila JH, Pukkila M, Hagstrom J, Laranne J, Soini Y, Kosma VM, Koivunen P, Kelner N, Kowalski LP, Grenman R, Leivo I, Laara E and Salo T (2015). For early-stage oral tongue cancer, depth of invasion and worst pattern of invasion are the strongest pathological predictors for locoregional recurrence and mortality. *Virchows Arch* **467**: 39-46.

Almangush A, Bello IO, Keski-Santti H, Makinen LK, Kauppila JH, Pukkila M, Hagstrom J, Laranne J, Tommola S, Nieminen O, Soini Y, Kosma VM, Koivunen P, Grenman R, Leivo I and Salo T (2014). Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. *Head Neck* **36**: 811-8.

Almangush A, Heikkinen I, Bakhti N, Makinen LK, Kauppila JH, Pukkila M, Hagstrom J, Laranne J, Soini Y, Kowalski LP, Grenman R, Haglund C, Makitie AA, Coletta RD, Leivo I and Salo T (2018). Prognostic impact of tumour-stroma ratio in early-stage oral tongue cancers. *Histopathology* **72**: 1128-1135.

This article is protected by copyright. All rights reserved

Bello IO, Vered M, Dayan D, Dobriyan A, Yahalom R, Alanen K, Nieminen P, Kantola S, Laara E and Salo T (2011). Cancer-associated fibroblasts, a parameter of the tumor microenvironment, overcomes carcinoma-associated parameters in the prognosis of patients with mobile tongue cancer. *Oral Oncol* **47**: 33-8.

Brandwein-Gensler M, Smith RV, Wang B, Penner C, Theilken A, Broughel D, Schiff B, Owen RP, Smith J, Sarta C, Hebert T, Nason R, Ramer M, DeLacure M, Hirsch D, Myssiorek D, Heller K, Prystowsky M, Schlecht NF and Negassa A (2010). Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol* **34**: 676-88.

Brierley J, D., Gospodarowicz M, K. and Wittekind C (2017). TNM Classification of Malignant Tumours. 8th Edition. John Wiley & Sons, Ltd: UK.

Campbell BR, Netterville JL, Sinard RJ, Mannion K, Rohde SL, Langerman A, Kim YJ, Lewis JS, Jr. and Lang Kuhs KA (2018). Early onset oral tongue cancer in the United States: A literature review. *Oral Oncol* **87**: 1-7.

Farquhar DR, Tanner AM, Masood MM, Patel SR, Hackman TG, Olshan AF, Mazul AL and Zevallos JP (2018). Oral tongue carcinoma among young patients: An analysis of risk factors and survival. *Oral Oncol* **84**: 7-11.

Fonseca FP, Coletta RD, Azevedo MB, Prado Ribeiro AC, Pires Soubhia AM, Miyahara GI, Carlos R, Farthing P, Hunter KD, Speight PM, Vargas PA, Almeida OP, Lopes MA and Santos-Silva AR (2014). Stromal myofibroblasts in squamous cell carcinoma of the tongue in young patients - a multicenter collaborative study. *Oral surgery, oral medicine, oral pathology and oral radiology* **118**: 483-9.

Gu X, Coates PJ, Boldrup L, Wang L, Krejci A, Hupp T, Fahraeus R, Norberg-Spaak L, Sgaramella N, Wilms T and Nylander K (2019). Copy number variation: A prognostic marker for young patients with squamous cell carcinoma of the oral tongue. *J Oral Pathol Med* **48**: 24-30.

Heikkinen I, Bello IO, Wahab A, Hagstrom J, Haglund C, Coletta RD, Nieminen P, Makitie AA, Salo T, Leivo I and Almangush A (2019). Assessment of Tumor-infiltrating Lymphocytes Predicts the Behavior of Early-stage Oral Tongue Cancer. *Am J Surg Pathol*.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Kademani D, Bell RB, Bagheri S, Holmgren E, Dierks E, Potter B and Homer L (2005). Prognostic factors in intraoral squamous cell carcinoma: the influence of histologic grade. *J Oral Maxillofac Surg* **63**: 1599-605.

Llewellyn CD, Linklater K, Bell J, Johnson NW and Warnakulasuriya S (2004). An analysis of risk factors for oral cancer in young people: a case-control study. *Oral Oncol* **40**: 304-13.

Muller S, Pan Y, Li R and Chi AC (2008). Changing trends in oral squamous cell carcinoma with particular reference to young patients: 1971-2006. The Emory University experience. *Head Neck Pathol* **2**: 60-6.

Ng JH, Iyer NG, Tan MH and Edgren G (2017). Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. *Head Neck* **39**: 297-304.

Paderno A, Morello R and Piazza C (2018). Tongue carcinoma in young adults: a review of the literature. *Acta Otorhinolaryngol Ital* **38**: 175-180.

Pickering CR, Zhang J, Neskey DM, Zhao M, Jasser SA, Wang J, Ward A, Tsai CJ, Ortega Alves MV, Zhou JH, Drummond J, El-Naggar AK, Gibbs R, Weinstein JN, Wheeler DA, Wang J, Frederick MJ and Myers JN (2014). Squamous cell carcinoma of the oral tongue in young non-smokers is genomically similar to tumors in older smokers. *Clinical cancer research : an official journal of the American Association for Cancer Research* **20**: 3842-8.

Santos-Silva AR, Ribeiro AC, Soubhia AM, Miyahara GI, Carlos R, Speight PM, Hunter KD, Torres-Rendon A, Vargas PA and Lopes MA (2011). High incidences of DNA ploidy abnormalities in tongue squamous cell carcinoma of young patients: an international collaborative study. *Histopathology* **58**: 1127-35.

Tam S, Amit M, Zafereo M, Bell D and Weber RS (2019). Depth of invasion as a predictor of nodal disease and survival in patients with oral tongue squamous cell carcinoma. *Head Neck* **41**: 177-184.

Taybos G (2003). Oral changes associated with tobacco use. *Am J Med Sci* **326**: 179-82.

This article is protected by copyright. All rights reserved

Accepted Article

Table 1: Frequency and percentage distributions of various tumor-related epithelial and stromal histopathologic characteristics among young (≤45 years) and old patients (>60 years).

Variable	Young (≤45 yrs) (n=42)	Old (>60 yrs) (n=42)	*P* value*
Tumor grade			0.948
Well-differentiated	13 (31%)	15 (36%)	
Moderately-differentiated	20 (48%)	18 (43%)	
Poorly-differentiated	9 (21%)	9 (21%)	
Depth of invasion#			0.804
Superficial	14 (33%)	16 (38%)	
Deep	28 (67%)	26 (69%)	
Perineural invasion			0.727
Absent	38 (91%)	36 (86%)	
Present	4 (9%)	6 (14%)	
Tumor budding#			0.077
Low intensity	24 (57%)	32 (76%)	
High intensity	18 (43%)	10 (24%)	
Histologic risk score##			0.225
Low-risk (0)	1 (2.4%)	1 (2.4%)	
Intermediate-risk (1-2)	9 (21.4%)	14 (33.3%)	
High-risk (≥3)	32 (76.2)	27 (64.3%)	
Worst pattern of invasion			0.065
Cohesive	6 (14%)	13 (31%)	
Infiltrative	36 (86%)	29 (69%)	
Tumor - stroma ratio (TSR)			0.180
Low	27 (64%)	33 (79%)	
High	15 (36%)	9 (31%)	
Tumor-infiltrating lymphocytes			> 0.999
Low response	6 (14%)	7 (17%)	

This article is protected by copyright. All rights reserved

High response	36 (86%)	34 (83%)

[*] *P* value of McNemar test (2x2 table) or McNemar-Bowker (3x3 table) test.

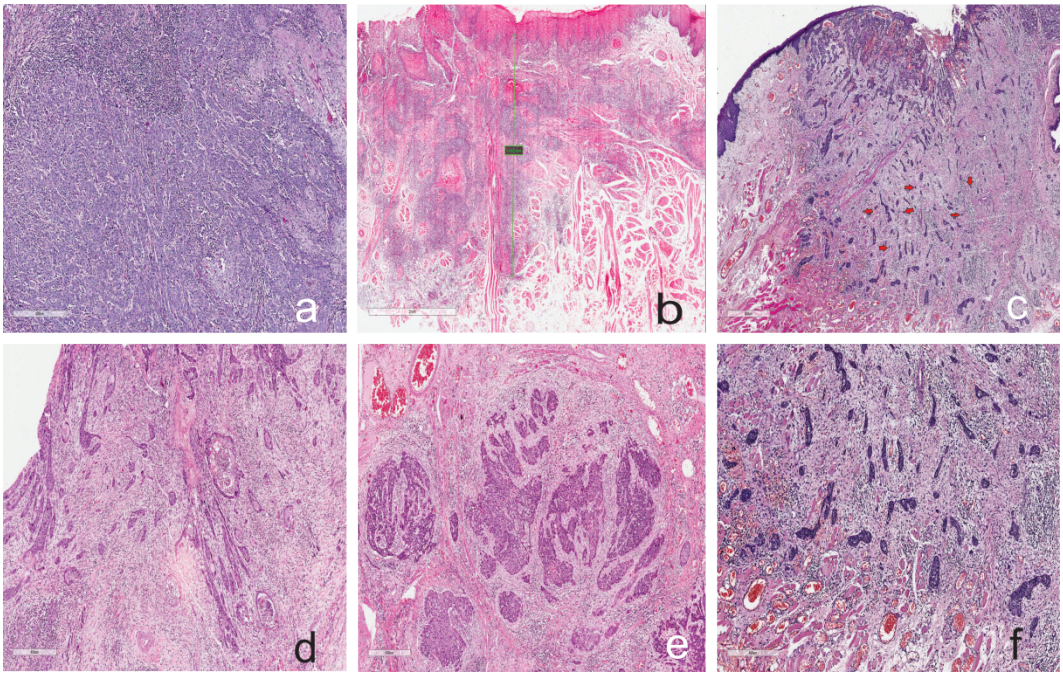
[#]Depth of invasion was classified as superficial when less than 4mm. High tumor budding was defined as presence of 5 or more tumor buds (see figure 1) at the invasive front of the tumor. Worst pattern of invasion, TSR and TIL are briefly explained in Figure 1.

[##] Histologic risk score comprises both tumor cell-related and stromal components (WPOI, lymphocytic host response and perineural invasion). Final score used to categorize cases for HRS are in parenthesis.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article



odi_13288_f1.tif

This article is protected by copyright. All rights reserved